PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference MJL/B45309	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/08569	International filing date *(day/month/year)* 31.07.2003	Priority date *(day/month/year)* 02.08.2002
International Patent Classification (IPC) or both national classification and IPC C12N15/00		
Applicant GLAXOSMITHKLINE BIOLOGICALS SA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
24.02.2004	15.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Noë, V Telephone No. +31 70 340-4181

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/08569

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-28 as originally filed

Claims, Numbers

1-53 received on 18.10.2004 with letter of 18.10.2004

Drawings, Sheets

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-53
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-53
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-53
	No:	Claims	

2. Citations and explanations

see separate sheet

V. Reasoned statement (Continuation)

2.1 CITATIONS

Reference is made to the following documents:

D1: WO 01/09350 A (DALEMANS WILFRIED L J ;SMITHKLINE BEECHAM BIOLOG (BE); THIRY GEORG) 8 February 2001 (2001-02-08)
D2: WO 01/19960 A (WOMENS & CHILDRENS HOSPITAL ;LUMINIS PTY LTD (AU)) 22 March 2001 (2001-03-22)

3 NOVELTY (Art. 33(2) PCT)

3.1 The present application satisfies the criterion set forth in Article 33(2) PCT because the subject-matter of claims 1-53 is novel in respect of prior art as defined in the regulations (Rule 64(1)-(3) PCT).

4 INVENTIVE STEP (Art. 33(3) PCT)

4.1 For inventive step analysis of claim 1, relating to a process of making a genetically engineered neisserial strain with an L2 or L3 LOS immunotype of reduced phase variability for manufacture of an immunogenic composition, D1 is considered to represent the most relevant state of the art and discloses a process for making recombinant neisserial strains for the manufacture of an immunogenic composition. The subject-matter of claim 1 differs in that a process for making a genetically engineered neisserial strain with reduced phase variability is claimed.

4.2 The problem to be solved by the subject matter of claim 1 may therefore be regarded as the provision of a process for making an alternative recombinant neisserial strain. The solution would be a process for making a genetically engineered neisserial strain with reduced phase variability.

4.3 This solution is considered as involving an inventive step (Article 33(3) PCT) because, although D2 discloses a method to stabilize the expression of lgtA, LgtC

and LgtD by mutation of the poly G tract, it would not be obvious for the person skilled in the art to use the teachings of D2 in order to obtain a method for producing a neisserial strain with reduced LOS phase variability for the manufacture of an immunogenic composition, taking into account that D2 does not disclose the fact that mutations of Lgt genes are the cause of L2 or L3 LOS phase variability. Therefore, the subject-matter of claim 1 and dependent claims 2-31 is considered to be inventive.

4.4 The subject-matter of claims 32-53 is considered to involve an inventive step because the processes of claims 32-44 comprises the process of making a genetically engineered neisserial strain with a fixed L2 or L3 LOS immunotype for the manufacture of an immunogenic composition (claims 1-32) which is considered to be inventive (see reasoning above).